Year in Review 2020
Hepatocellular Carcinoma

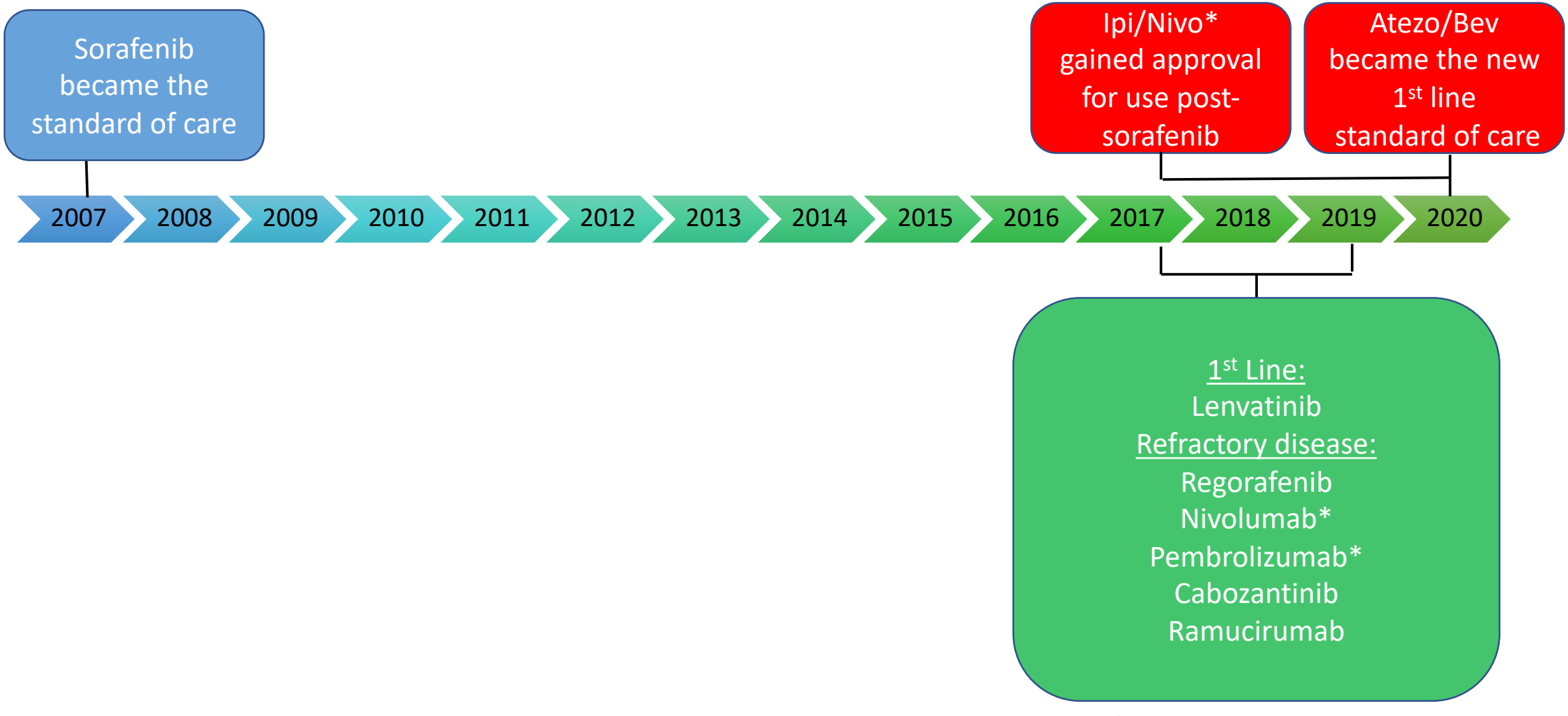
Lipika Goyal, MD, MPhil
Lead of the Liver Cancer Research Program
Massachusetts General Hospital Cancer Center
Assistant Professor
Harvard Medical School
Boston, Massachusetts

Agenda

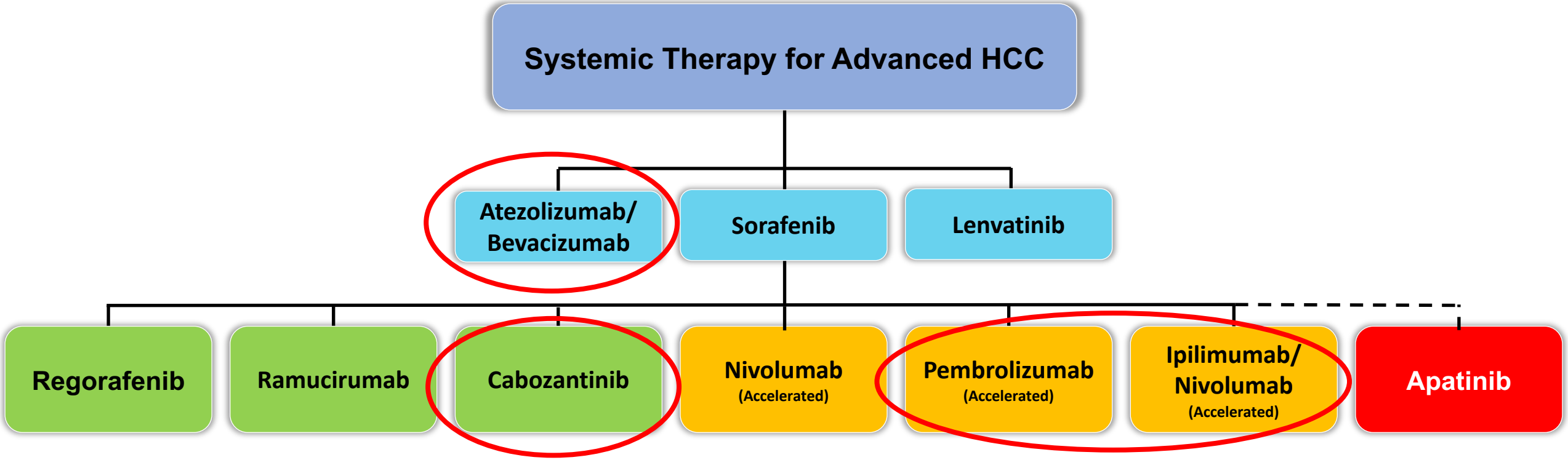
Module – Hepatocellular Carcinoma

1. Atezolizumab/Bevacizumab (IMbrave150)
2. Cabozantinib (CELESTIAL)
3. Pembrolizumab (KEYNOTE-224, KEYNOTE-240), Ipilimumab/Nivolumab (CheckMate 040)
4. Combination regimens on the horizon

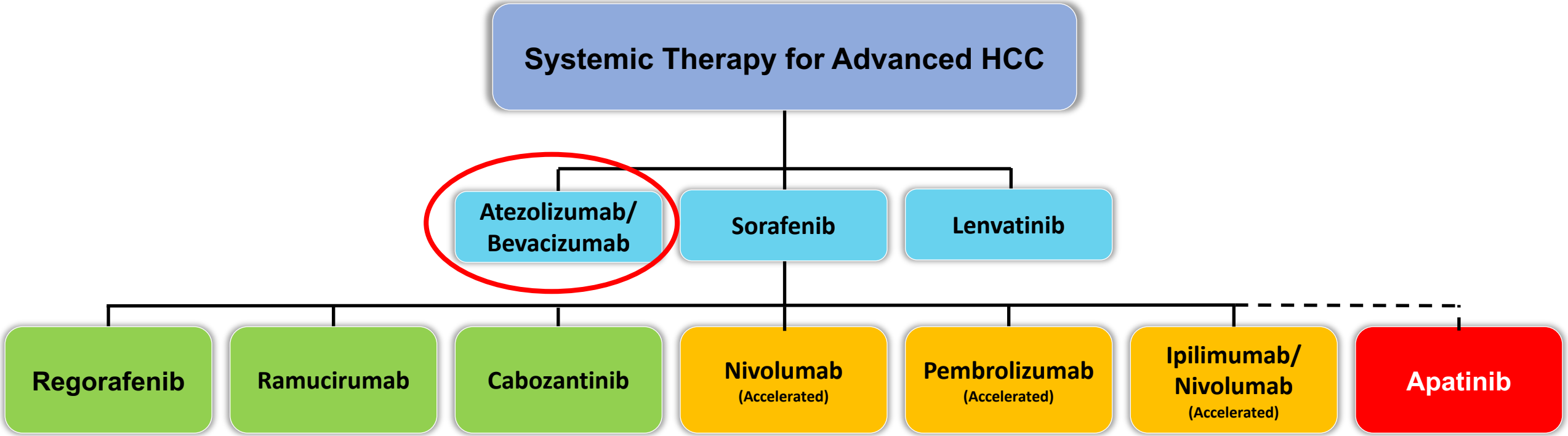
FDA Approved Systemic Therapy for Advanced HCC



*Accelerated Approval



Combination Treatments on the Horizon



Combination Treatments on the Horizon

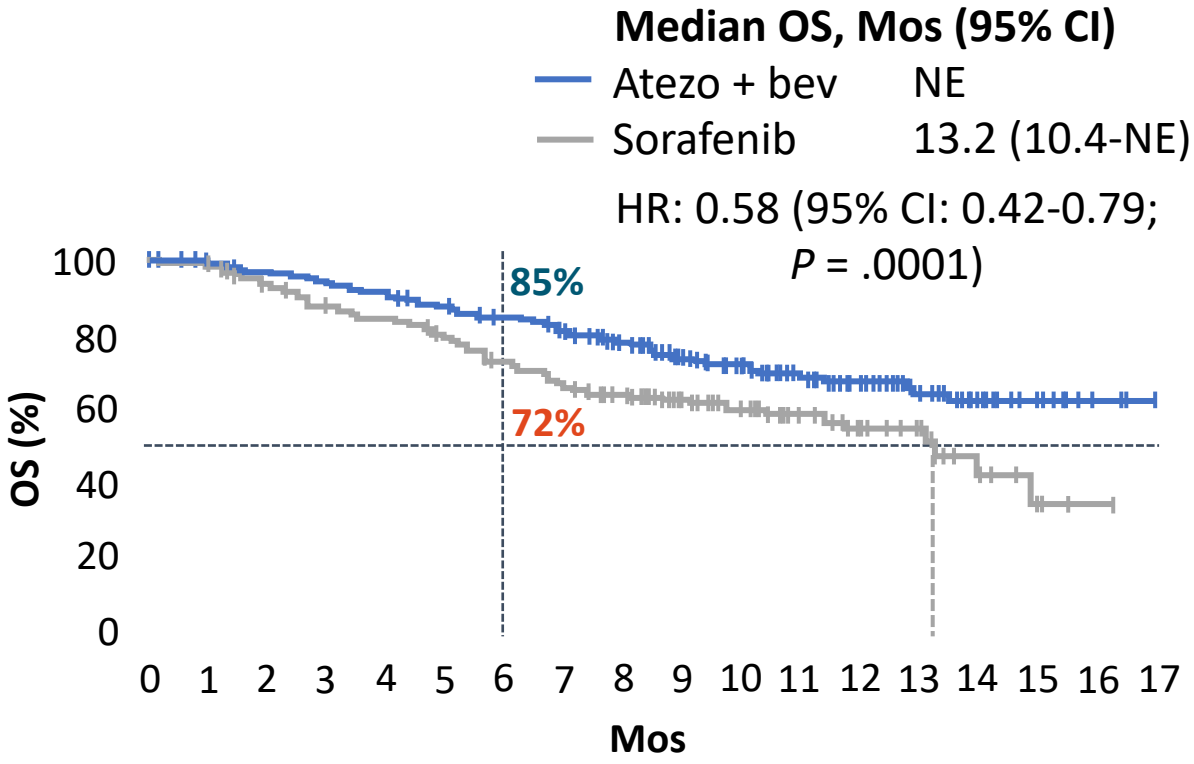
The NEW ENGLAND JOURNAL of MEDICINE

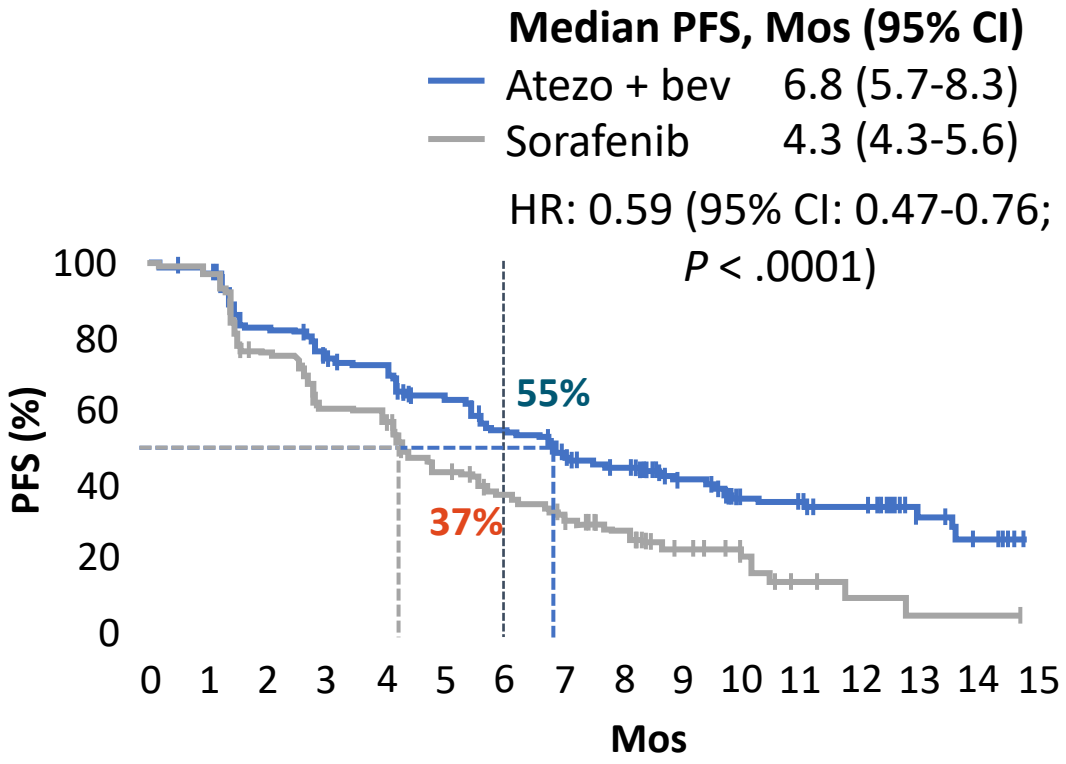
ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D., Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D., Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D., Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D., Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D., Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D., for the IMbrave150 Investigators*

IMbrave150: Atezo/Bevacizumab vs Sorafenib in Unresectable or Metastatic HCC





- ORR by modified RECIST with atezo + bev vs sorafenib: 33.2% vs 13.3%; CR rate, 10.2% vs 1.9%

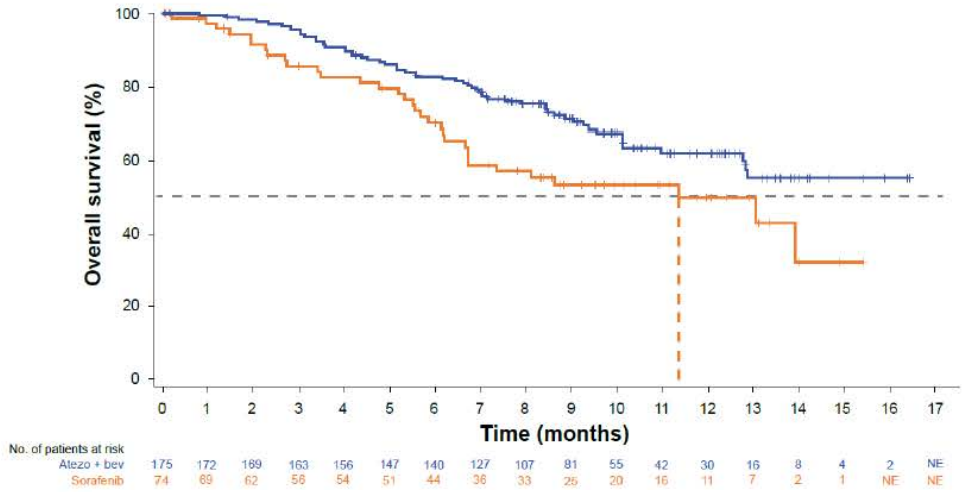
Median follow-up: 8.6 mos.

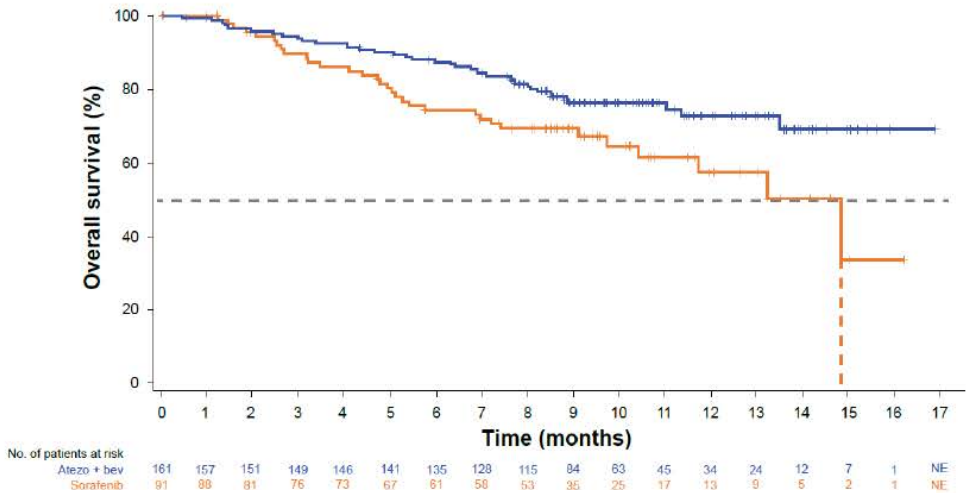
Finn, etal *NEJM.* 2020;382:1894.

IMbrave150: Atezo/Bevacizumab vs Sorafenib in Younger vs Older Patients Overall Survival Curves

	< 65 years	
	Atezo + bev (n = 175)	Sorafenib (n = 74)
Median OS, mo	NE	11.4
HR (95% CI)[a]	0.59 (0.38, 0.91)	

	≥ 65 years	
	Atezo + bev (n = 161)	Sorafenib (n = 91)
Median OS, mo	NE	14.9
HR (95% CI)[a]	0.58 (0.36, 0.92)	



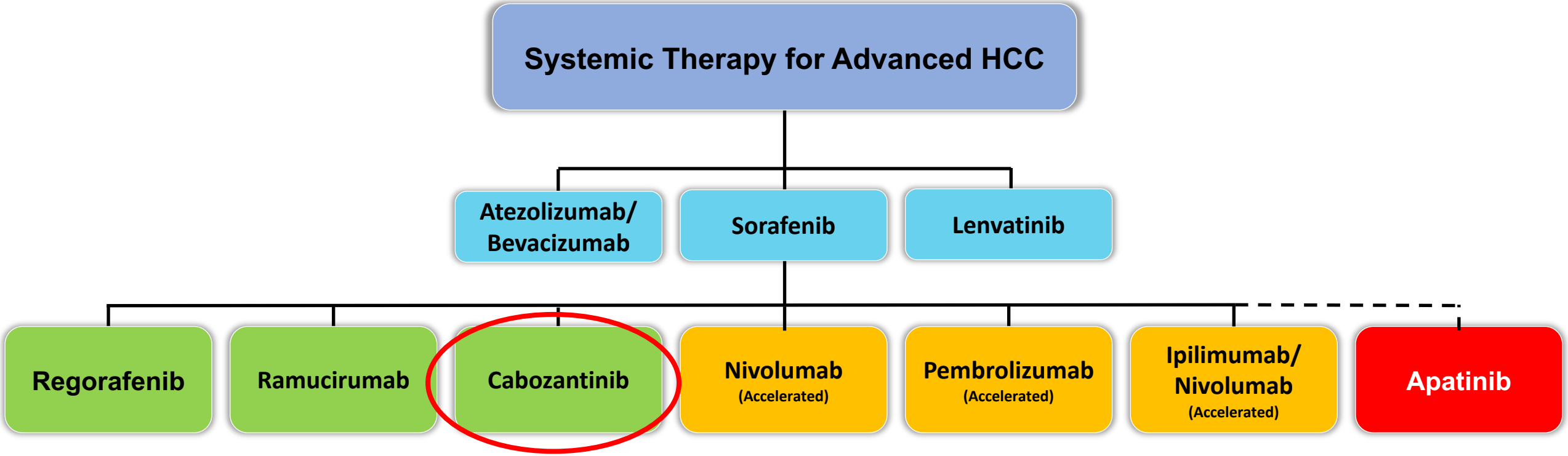


Characteristic	< 65 years		≥ 65 years	
	Atezo + bev (n = 175)	Sorafenib (n = 74)	Atezo + bev (n = 161)	Sorafenib (n = 91)
Response-evaluable population, n[b]	171	70	155	89
ORR, n (%)	49 (29)	7 (10)	40 (26)	12 (13)
CR, n (%)	11 (6)	0	7 (5)	0

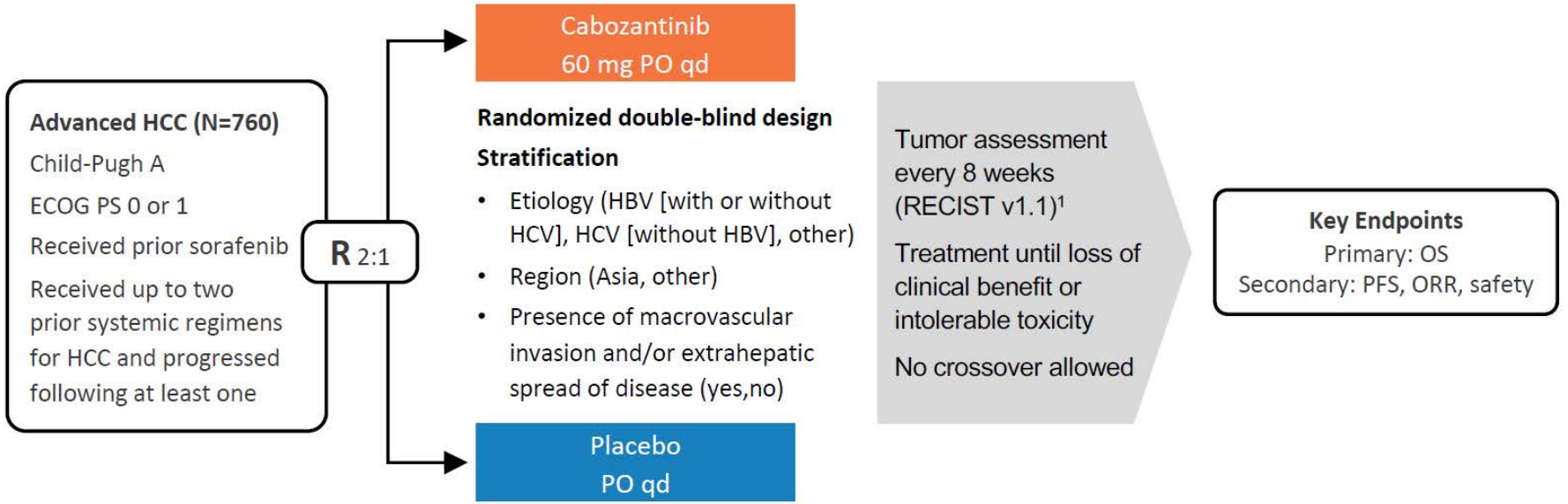
Li et al, *GI ESMO*, 2020

Conclusions: Atezolizumab/Bevacizumab for advanced HCC

- Clinical Implications:
  - Atezolizumab + Bevacizumab is a practice-changing regimen that improved PFS and OS for the first line treatment of advanced HCC
  - Atezolizumab + Bevacizumab had similar efficacy and safety for patients <65 yo and ≥ 65 yo
  - Side effects with Atezo+Bev: Hypertension, diarrhea, anorexia, proteinuria
- Future Directions:
  - Better predictive biomarkers are needed
  - Better understanding of subgroups likely to benefit
  - Multiple additional first-line trials to read out in 2021 and 2022


Systemic Therapy for Advanced HCC
Atezolizumab/ Bevacizumab
Sorafenib
Lenvatinib
Regorafenib
Ramucirumab
Cabozantinib
Nivolumab (Accelerated)
Pembrolizumab (Accelerated)
Ipilimumab/ Nivolumab (Accelerated)
Apatinib

CELESTIAL: Cabozantinib in Advanced HCC Subgroup analysis in Child Pugh B population



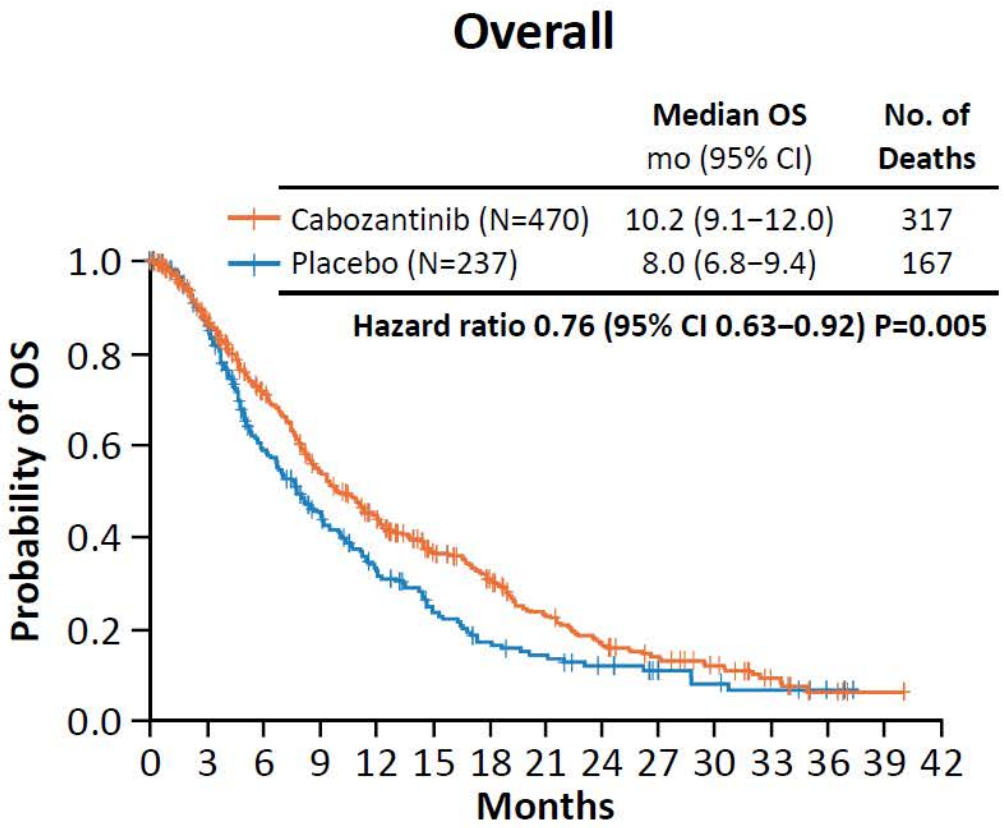
- **Outcomes were analyzed from randomization for the subgroup of patients who were Child-Pugh B on study by Week 8 (time of first Child-Pugh assessment post randomization)**
- **Child-Pugh class was assessed by the investigator**

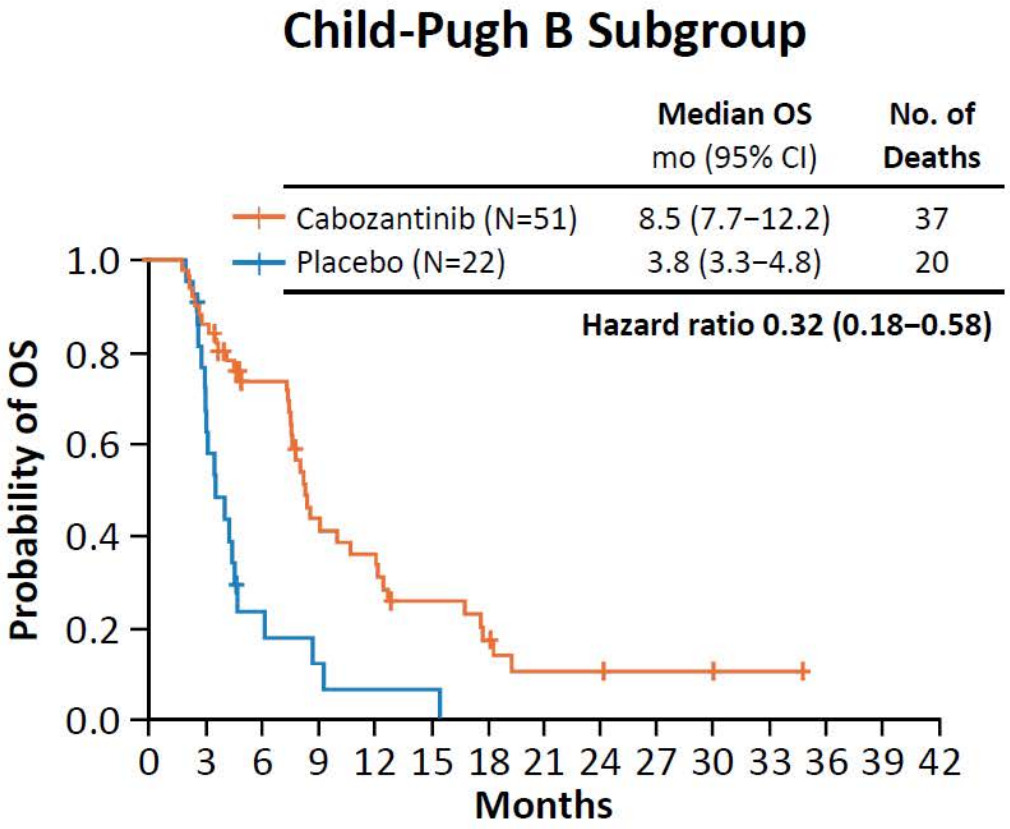
Evolution of cirrhosis to Child Pugh B at 8 weeks:
11% of cabozantinib group
9% of placebo group

Higher rates of:
- macrovascular invasion
- extrahepatic spread
- elevated AFP
- HBV and HCV

El-Khoueiry, et al, GI ESMO 2020

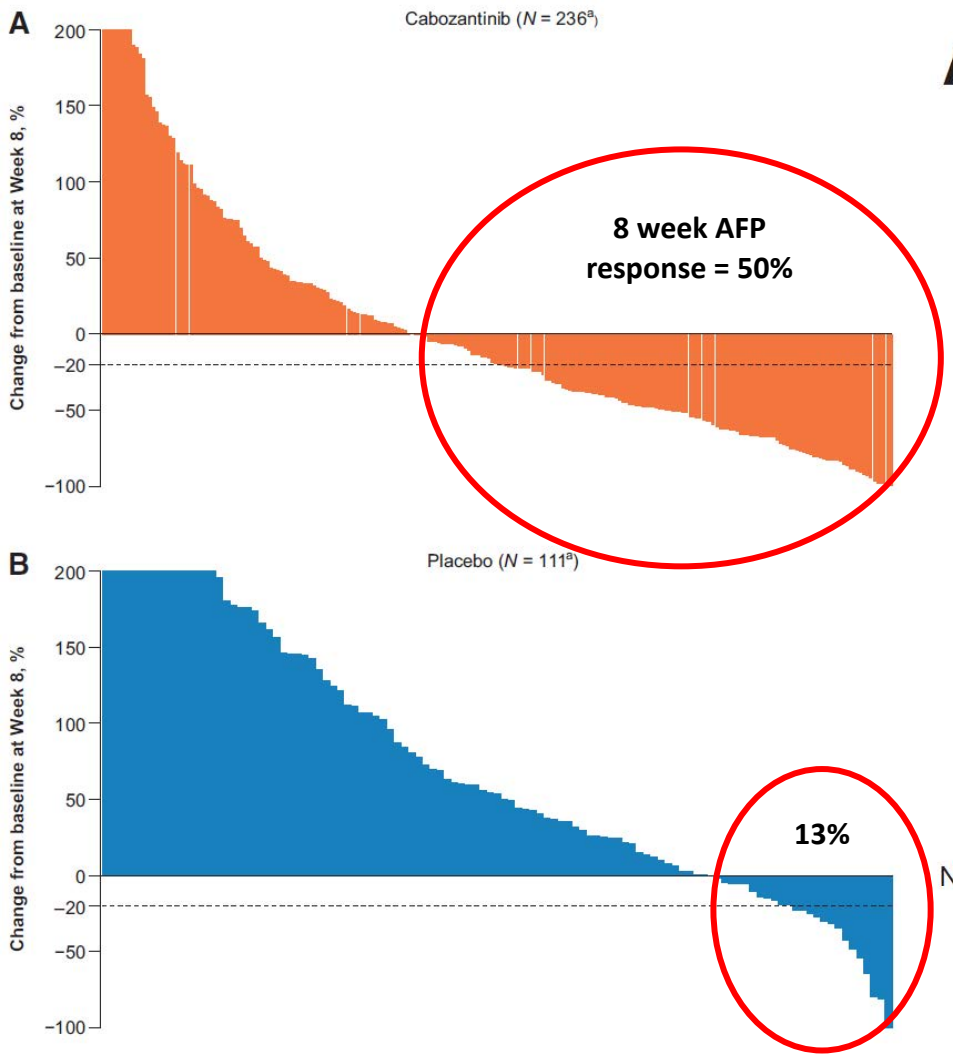
CELESTIAL: Cabozantinib in Advanced HCC Subgroup analysis in Child Pugh B population

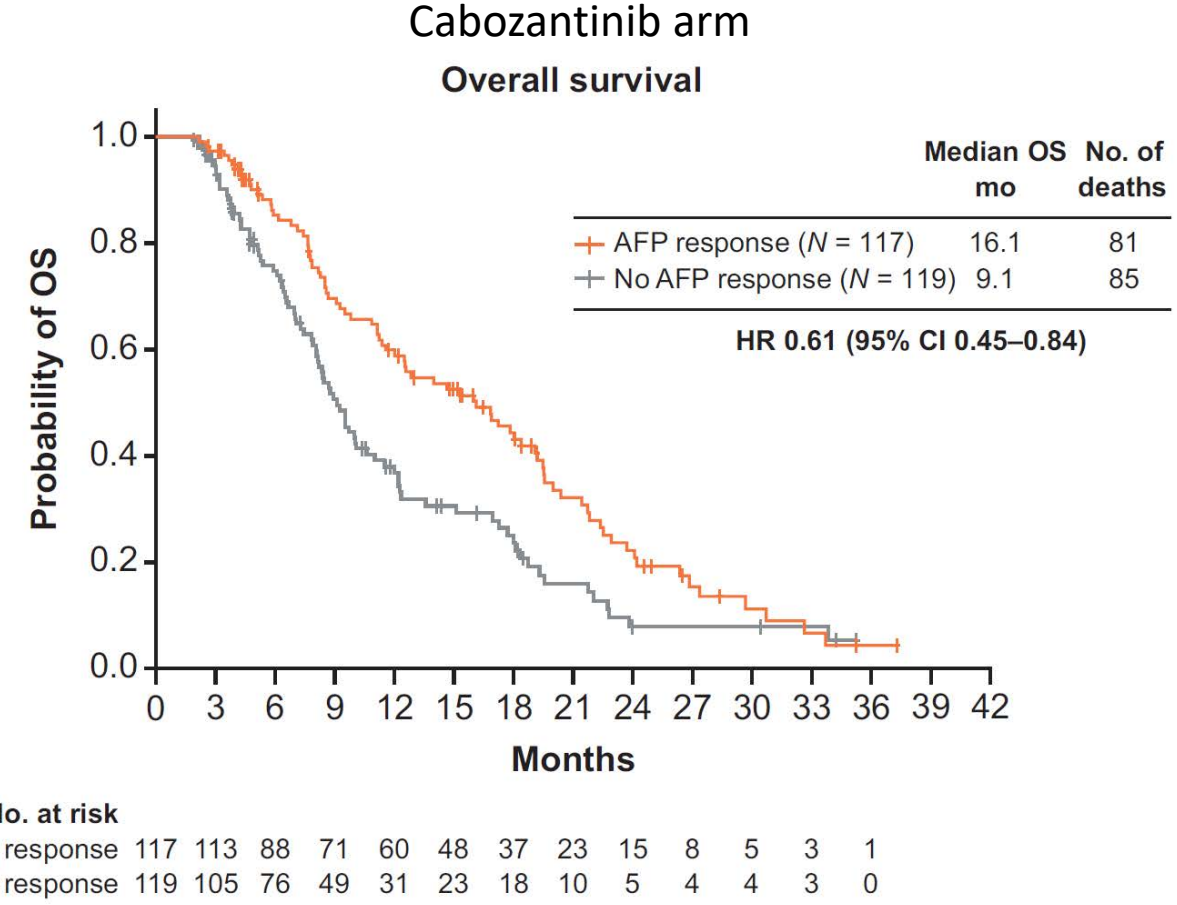




El-Khoueiry, et al, GI ESMO 2020

CELESTIAL: Cabozantinib in Advanced HCC
Subgroup analysis by baseline AFP and AFP response

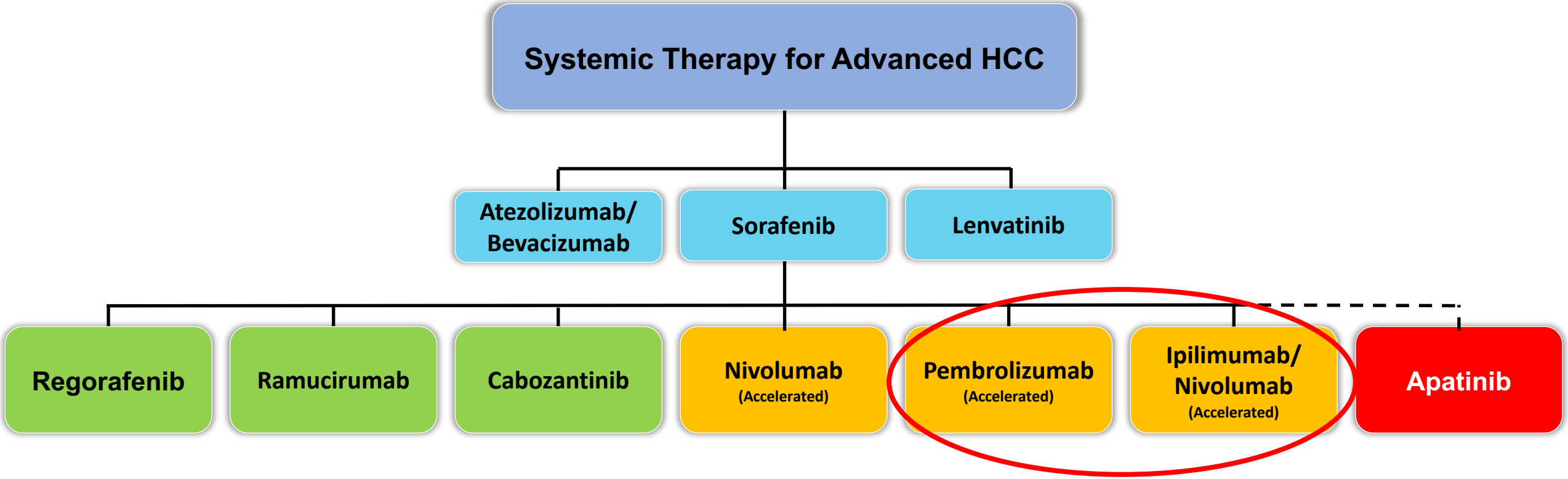




Kelley, et al, *CCR* 2020

Conclusions from exploratory subgroup analyses from the Phase III trial of Cabozantinib in HCC

- Clinical Implications:
  - Patients with liver function deterioration to Child Pugh B status at 8 weeks appeared to still derive OS benefit from cabozantinib
  - Patients with an AFP ≥ 400 ng appear to derive an OS benefit from cabozantinib
  - Patients with an AFP response of ≥ 20% at 8 weeks appear to derive more OS benefit from cabozantinib compared to the patients with no AFP response
- Future Directions:
  - Further studies are warranted in Child-Pugh B patients with HCC, a population with considerable unmet need
  - Additional predictive biomarkers are needed
  - Cabozantinib/IO combination trial results are awaited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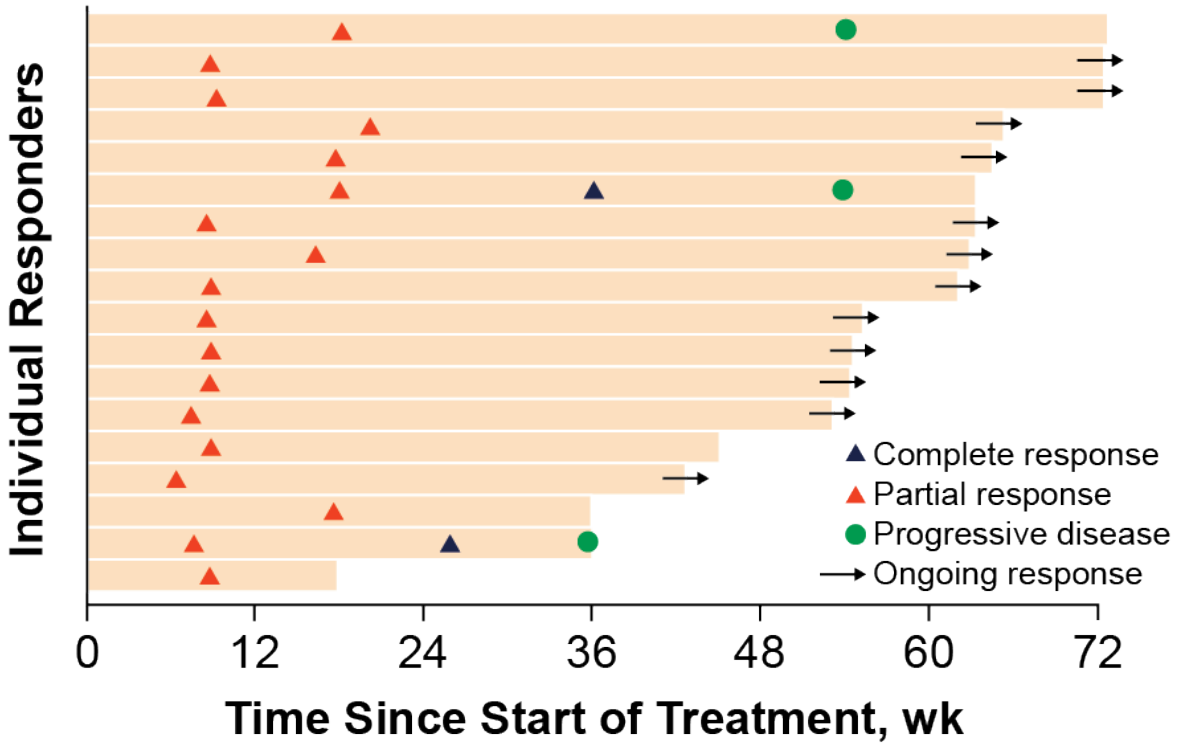
Apatinib

KEYNOTE-224: Phase II study of Pembrolizumab in advanced HCC



Median DOR not reached
Objective response: 17%

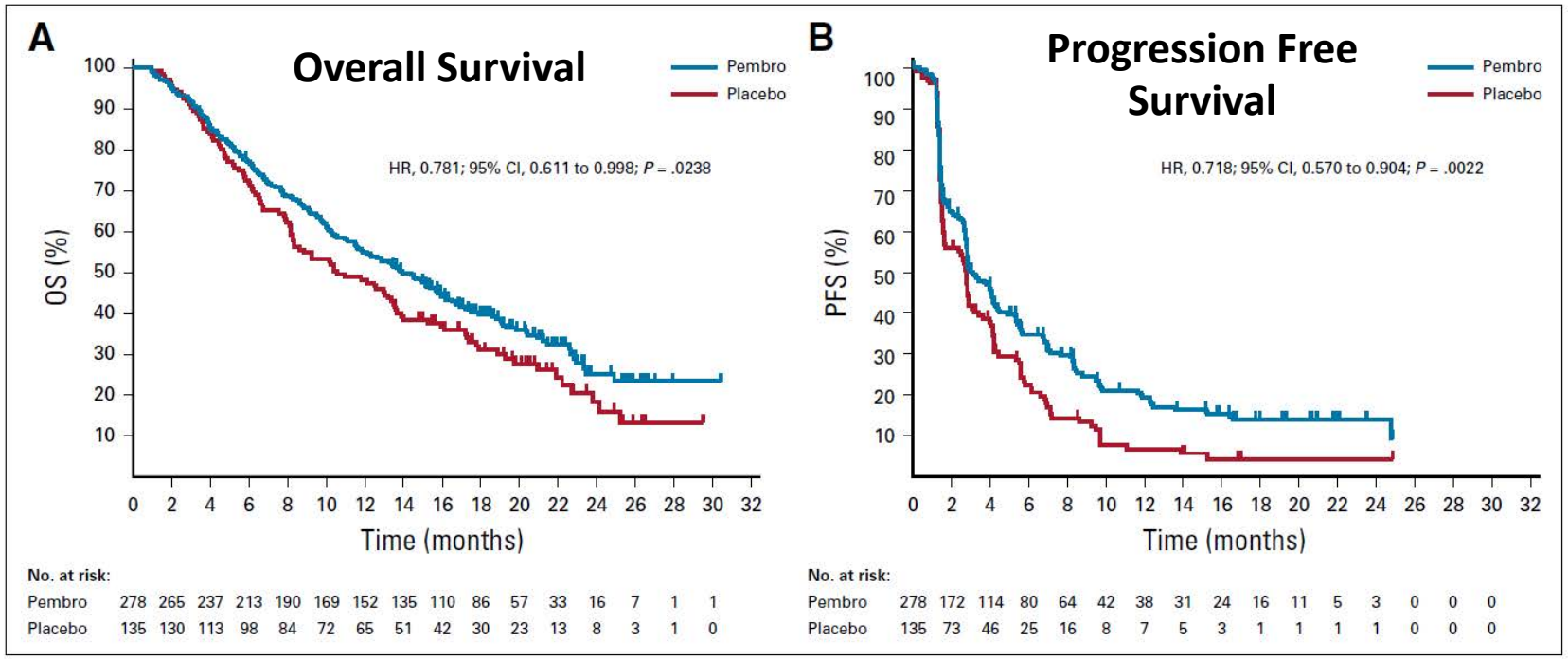
Zhu AX et al. *Lancet Oncol*. 2018;19:940-952.

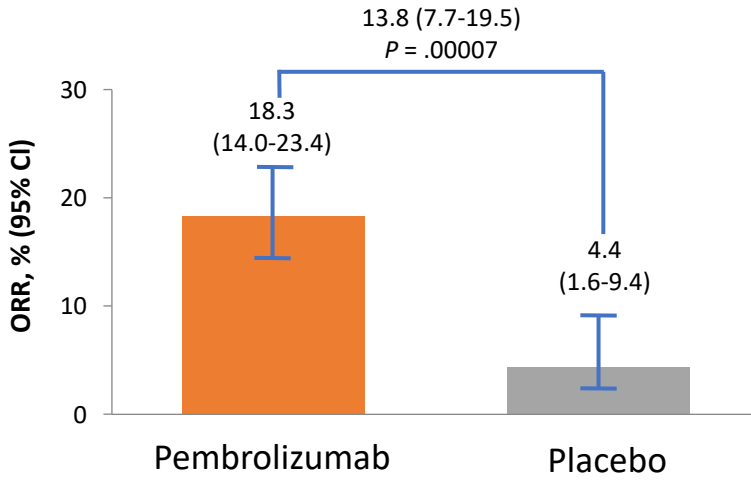
Updated data for KEYNOTE-224:

1. ORR improved from 17.3% to 18.3%
2. Duration of response ≥ 12 months improved from 61.4% to 77.0%
3. Complete response rate improved from 1.0% to 3.8%
4. Safety profile of pembrolizumab not significantly changed

Kudo, et al, *GI ASCO* 2020

KEYNOTE-240: Phase III study of Pembrolizumab vs Placebo in Advanced HCC





Pembrolizumab reduced the risk of death by 22% and improved PFS over placebo

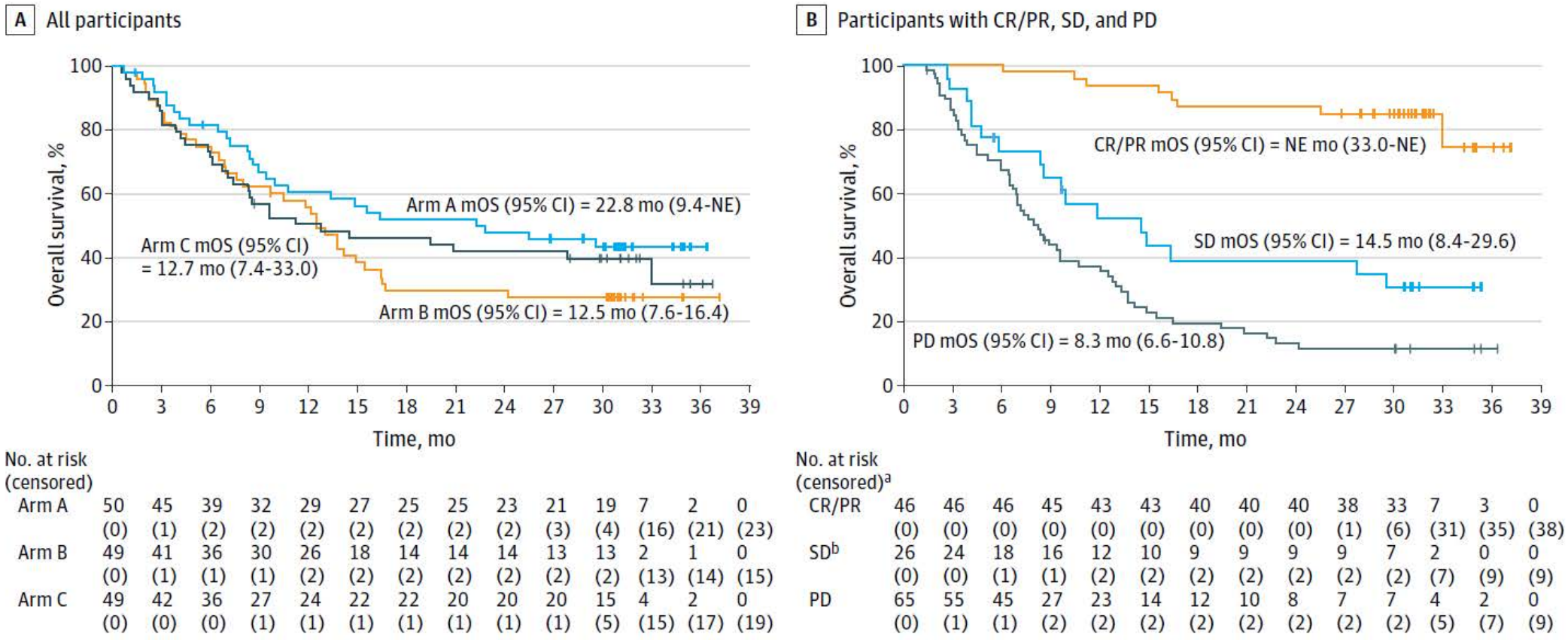
"These differences did not meet significance per the prespecified statistical plan"

Favorable risk-to-benefit ratio for pembrolizumab

Finn, et al *JCO* 2020

CheckMate 040: Ipilimumab and Nivolumab in advanced HCC after sorafenib

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for four doses, followed by nivolumab 240 mg alone every 2 weeks

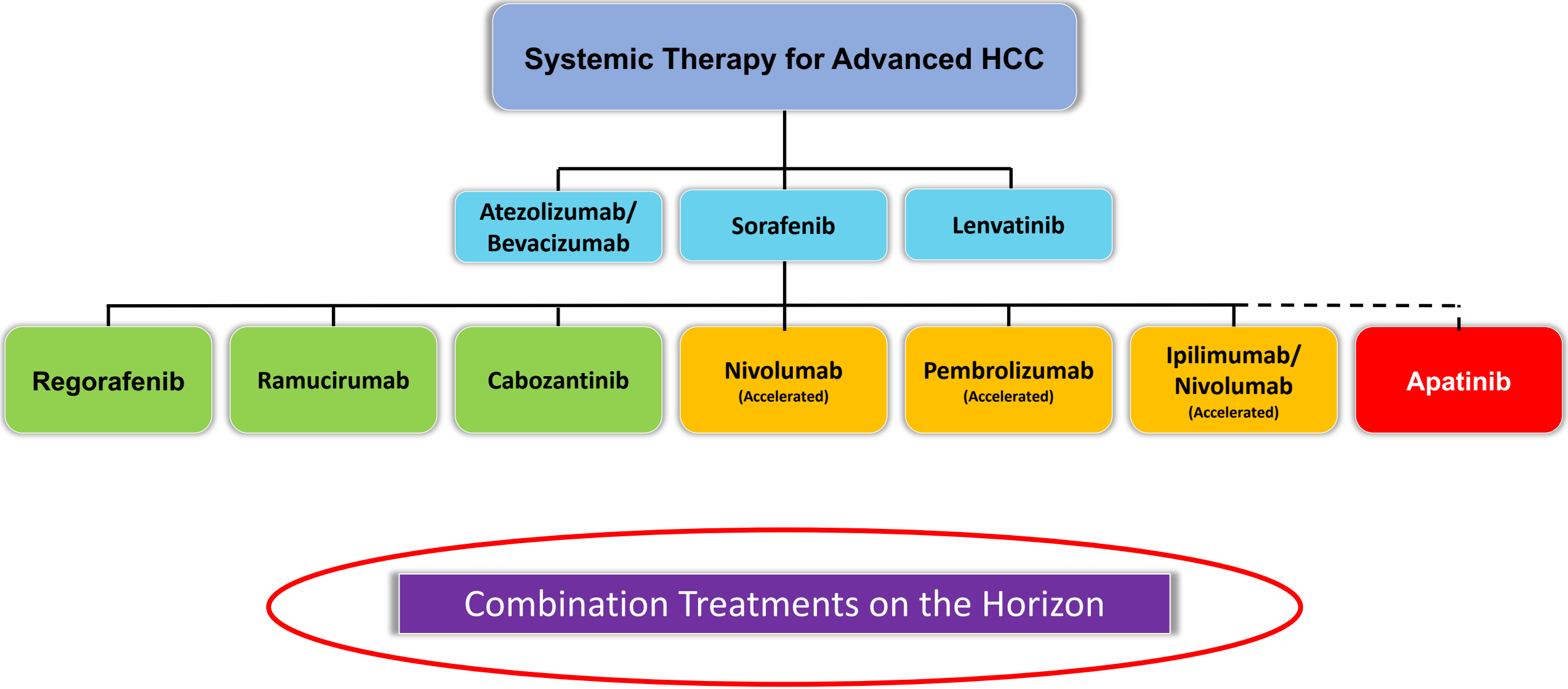


Objective Response Rate 32%

Yao, et al, *JAMA Onc*, 2020

Conclusions: Immunotherapy in 2nd line treatment of HCC

- Clinical Implications:
  - Nivolumab, Pembrolizumab, and Ipilimumab/Nivolumab have accelerated approval for advanced HCC post-sorafenib
  - They have response rates of 14-32% and responses are durable
- Future Directions:
  - Better predictive biomarkers are needed
  - Phase 3 study of pembrolizumab vs placebo as 2nd line therapy for advanced HCC is ongoing in the Asia-Pacific region (KEYNOTE-394)
  - Combination therapies of IO may ultimately prove more efficacious than single agent PD-1 inhibitors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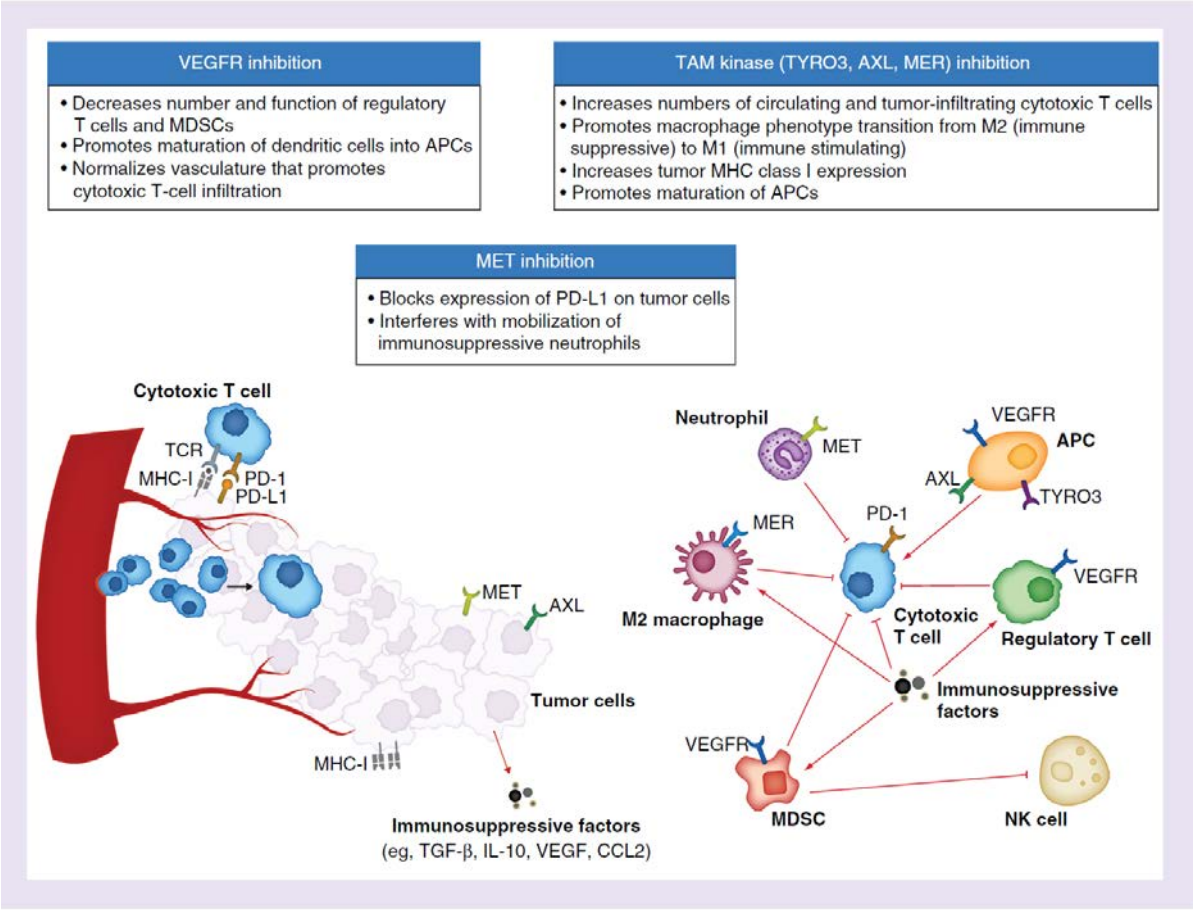
Combination Treatments on the Horizon

Rationale for Immunotherapy/TKI combinations

Lenvatinib targets:
VEGFR1-3, FGFR1-4, PDGFRα, KIT, RET



Cabozantinib targets:
VEGFR1-3, MET, TYRO3, AXL, MER

Kelley, et al, *Future Oncology,* 2020

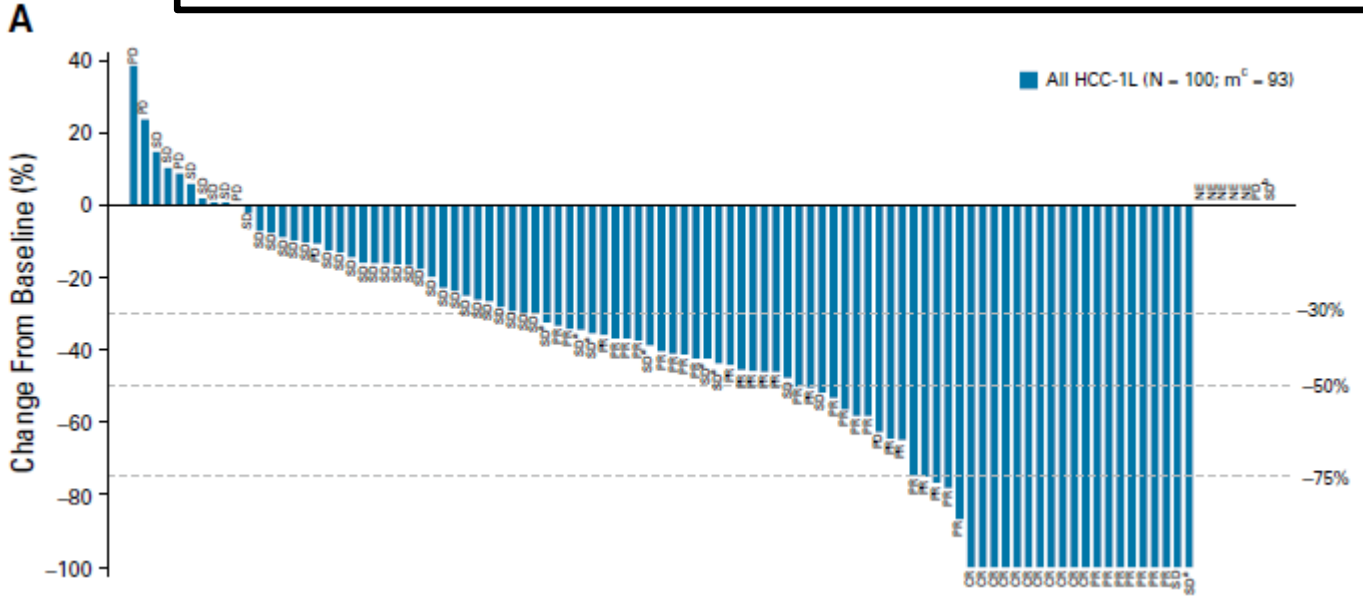
Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma

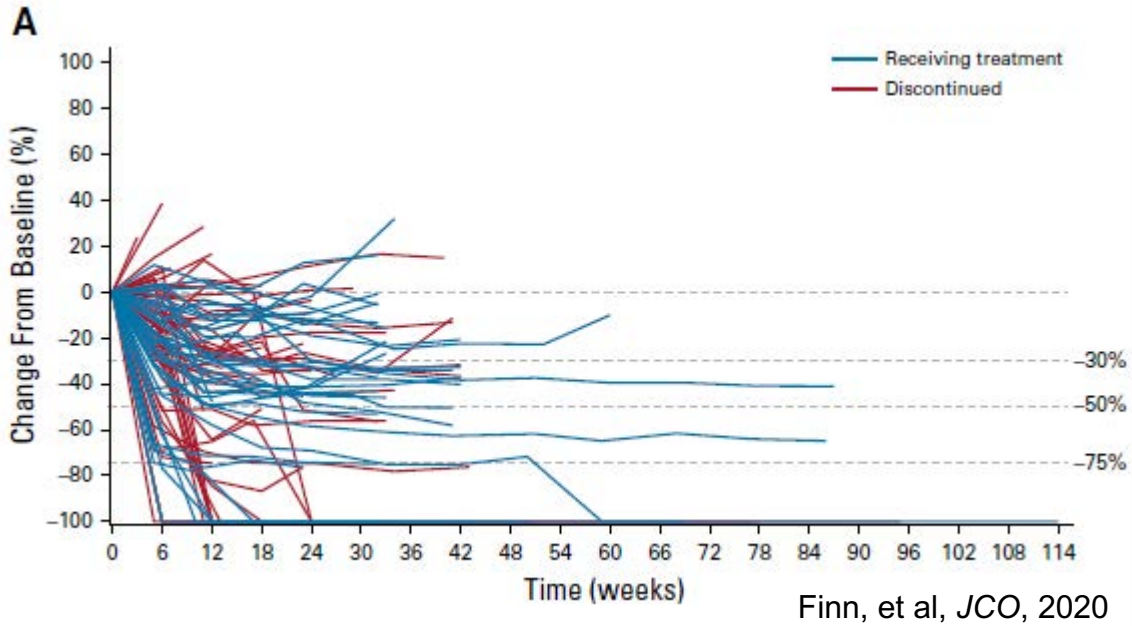
N=104 patients
No DLTs in DLT phase
Expansion phase in 1st line unresectable HCC
BCLC B (n=29), BCLC C (n=71)
Median follow-up: 10.6 months

Efficacy Parameter	RECIST v1.1	modified RECIST
ORR	36.0%	46.0%
Median Duration of Response	12.6 months	8.6 months
Median PFS	8.6 months	9.3 months

Median OS: 22 months

% change from Baseline in Sum of Target Lesions by **modified RECIST** (mRECIST) per independent imaging review





Finn, et al, *JCO*, 2020

Study 117: Phase Ib study of lenvatinib plus nivolumab in patients with unresectable HCC

Figure 1. Design of Phase 1b Study of Lenvatinib Plus Nivolumab in uHCC

Lenvatinib 12 or 8 mg/day (based on body weight) orally once daily + nivolumab 240 mg IV every 2 weeks

Part 1: DLT Evaluation
- n = 6
- Patients for whom no other appropriate therapy was available

Part 2: Expansion
- n = 24
- Patients with no prior systemic therapy for uHCC

Key Eligibility Criteria
- uHCC
- ≥ 1 Measurable target lesion
- BCLC stage B (not applicable for TACE) or C
- Child-Pugh class A
- ECOG performance status 0–1

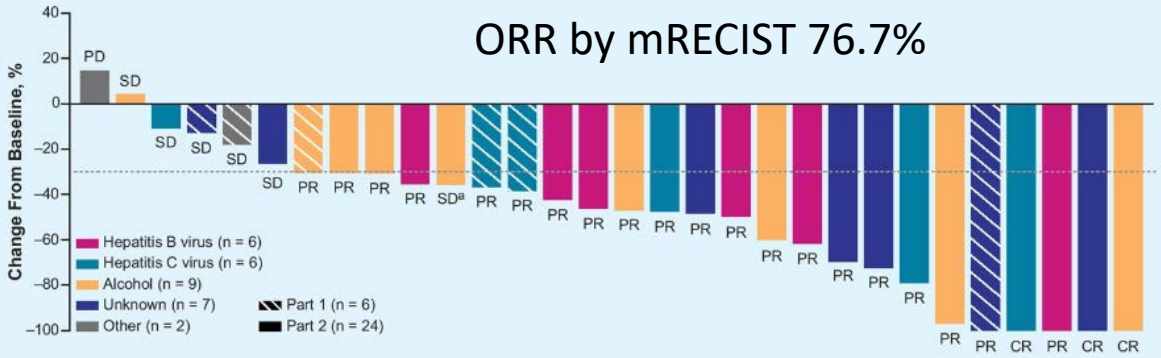
Primary end points
- Tolerability
- Safety of combination

Secondary end points
- ORR (mRECIST by investigator)
- Pharmacokinetic profiles of lenvatinib and nivolumab

BCLC, Barcelona Clinic Liver Cancer; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; mRECIST, modified Response Evaluation Criteria In Solid Tumors; ORR, objective response rate; TACE, transarterial chemoembolization; uHCC, unresectable hepatocellular carcinoma.

Figure 2. Percentage Changes From Baseline in Sums of Tumor Diameters by Investigator Assessment (mRECIST) Following Treatment With Lenvatinib Plus Nivolumab

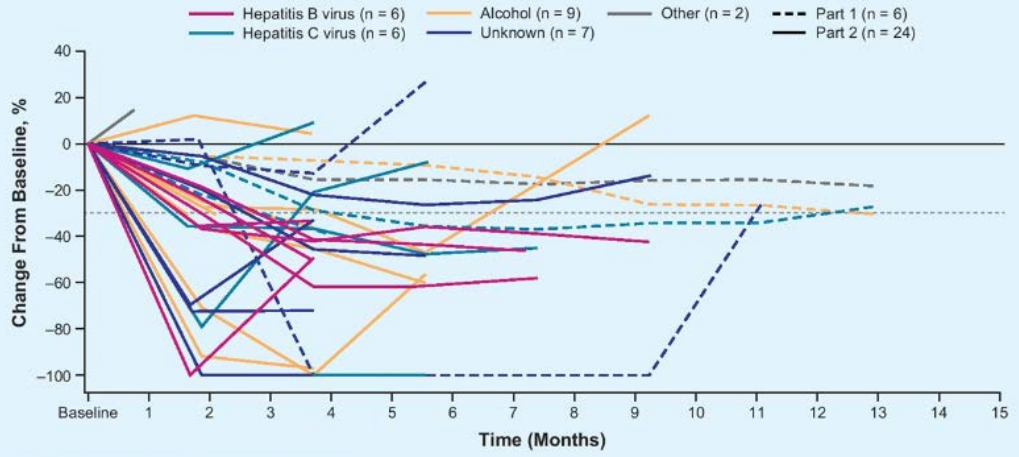
ORR by mRECIST 76.7%



[a]Patient experienced a 35% tumor shrinkage at the target lesion, but a nontarget lesion progressed at the same time.
CR, complete response; mRECIST, modified Response Evaluation Criteria In Solid Tumors; PD, progressive disease; PR, partial response; SD, stable disease.

- Tumor reductions appeared durable for most patients (**Figure 3** and **Figure 4**).

Figure 3. Percentage Change From Baseline in Sums of Diameters of Target Lesions Over Time by Investigator Assessment (mRECIST) Following Treatment With Lenvatinib Plus Nivolumab

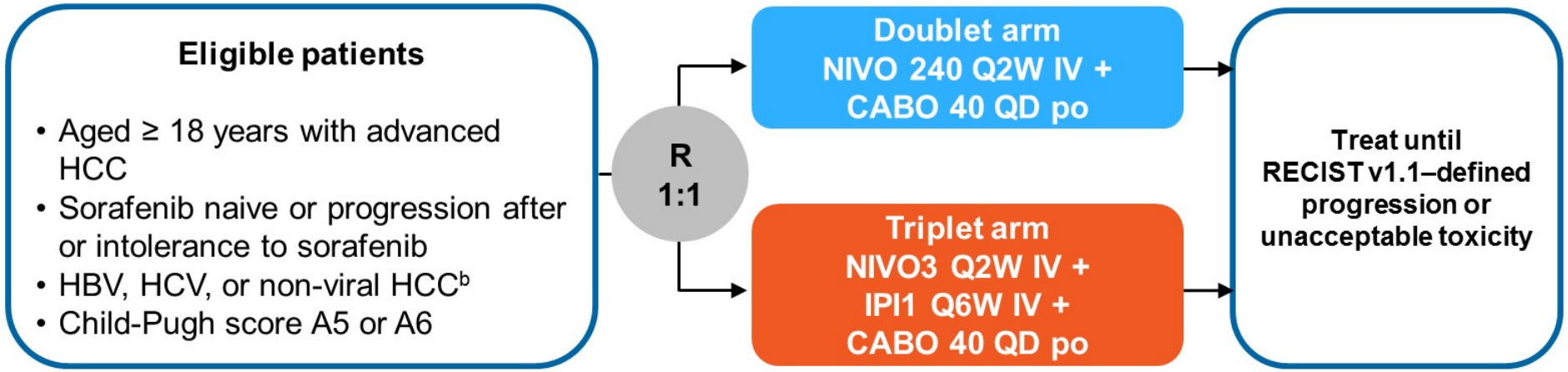


mRECIST, modified Response Evaluation Criteria In Solid Tumors.

Kudo, et al, *GI ASCO* 2020

CheckMate 040 Study Design[a]

Cabozantinib Cohort



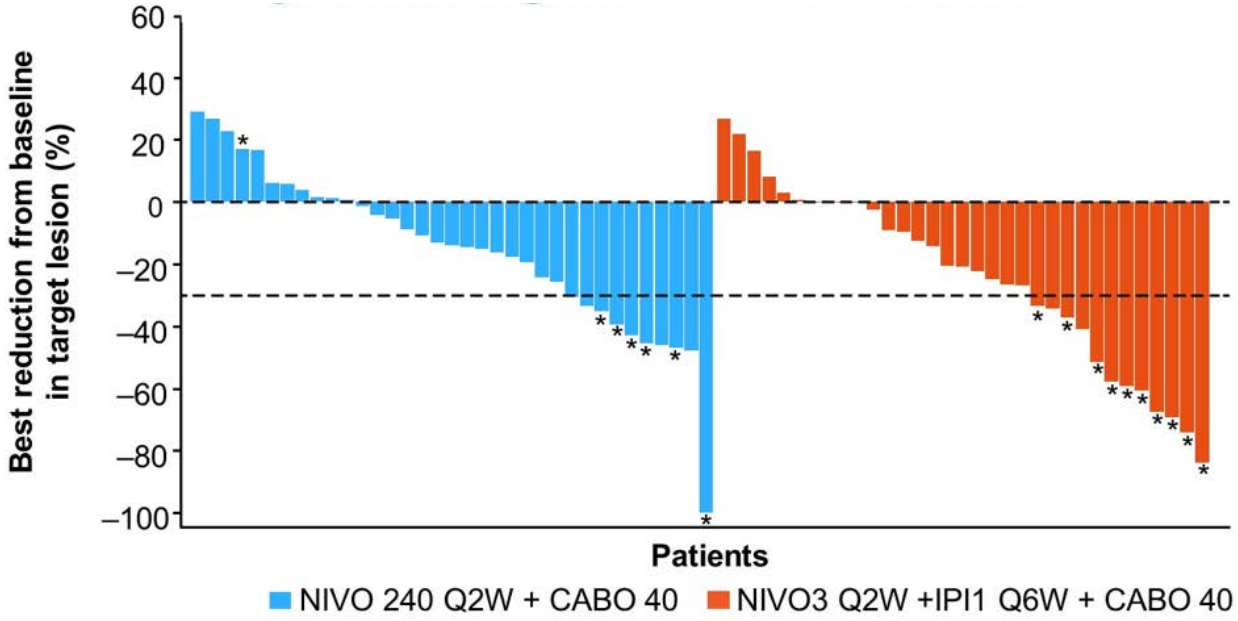
Primary endpoints
Safety and tolerability
ORR by investigator assessment

Secondary endpoints[c]
DCR, DOR, TTR, TTP, PFS, OS

Database lock: September 2019

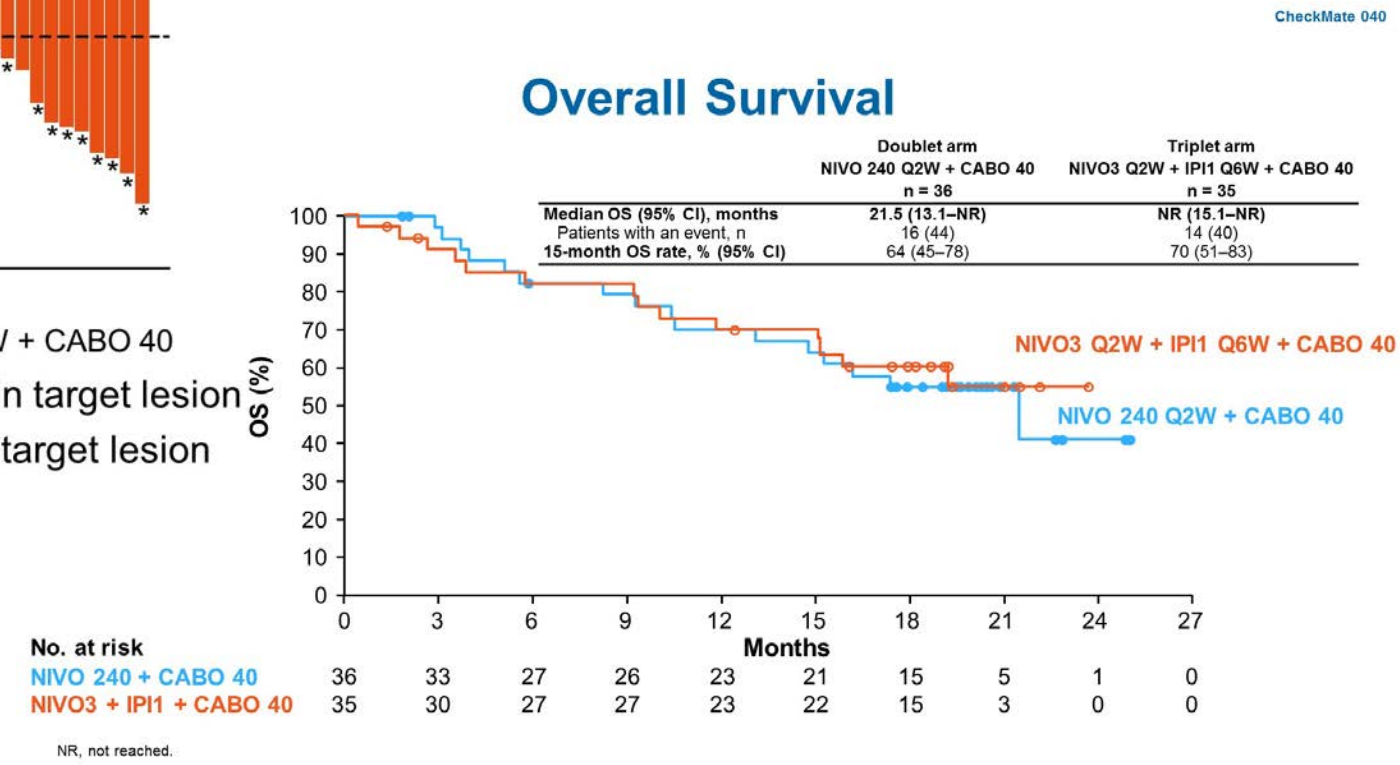
[a]ClinicalTrials.gov, NCT01658878; [b]Co-infection with HBV and HCV was an exclusion criterion; [c]Efficacy outcomes were evaluated by both investigator assessment and BICR.
BICR, blinded independent central review; CABO 40, cabozantinib 40 mg; DCR, disease control rate; DOR, duration of response; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IPI1, ipilimumb 1 mg/kg; IV, intravenous; NIVO 240, nivolumab 240 mg; NIVO3, nivolumab 3 mg/kg; PFS, progression-free survival; po, oral administration; Q2W, every 2 weeks; Q6W, every 6 weeks; QD, once daily; TTP, time to progression; TTR, time to response.

CheckMate 040: Nivo/Cabo vs Nivo/Ipi/Cabo



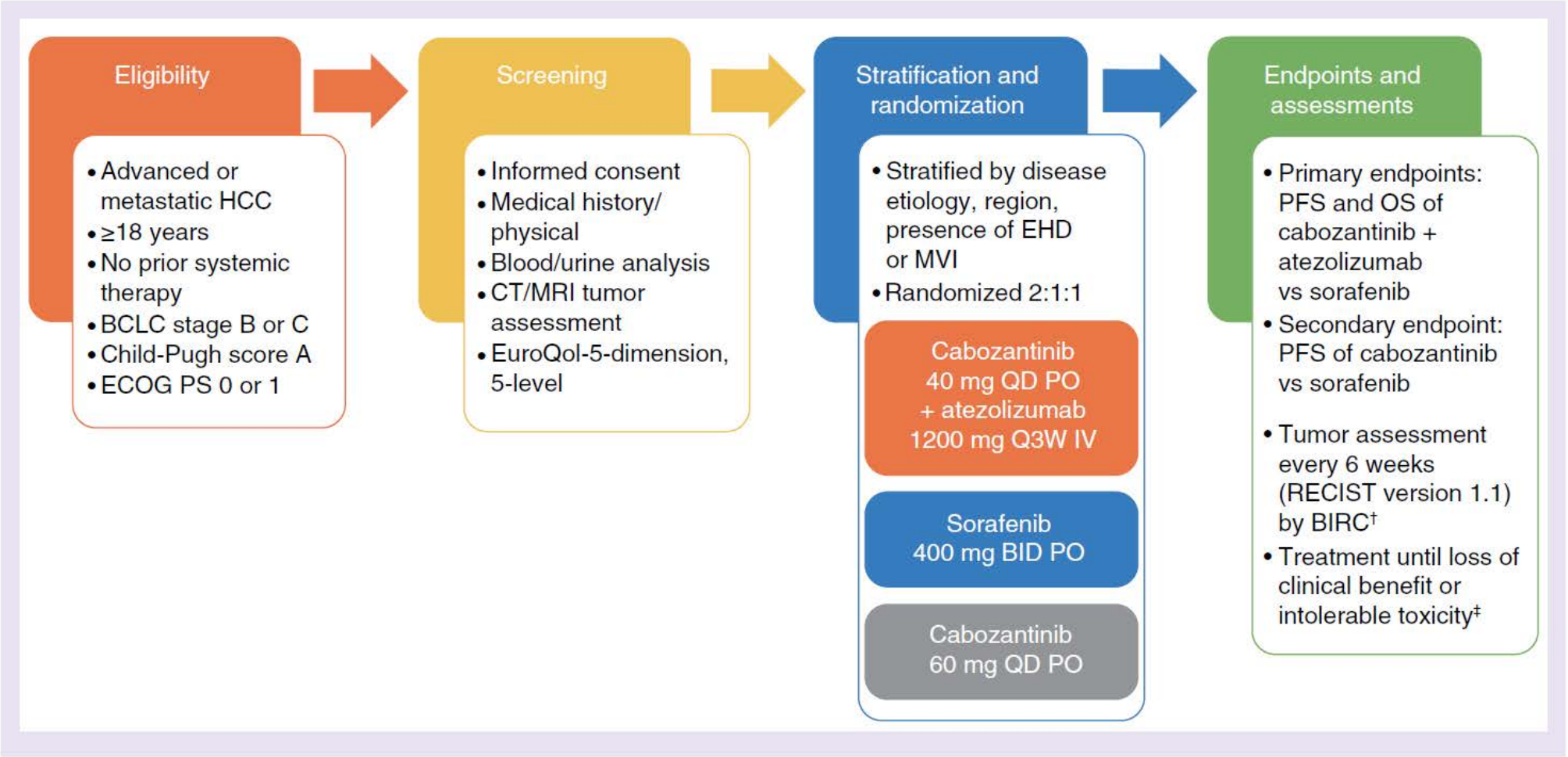
In the doublet arm, 24 of 35 patients (68.6%) had a decrease in target lesion

In the triplet arm, 23 of 33 patients (69.7%) had a decrease in target lesion



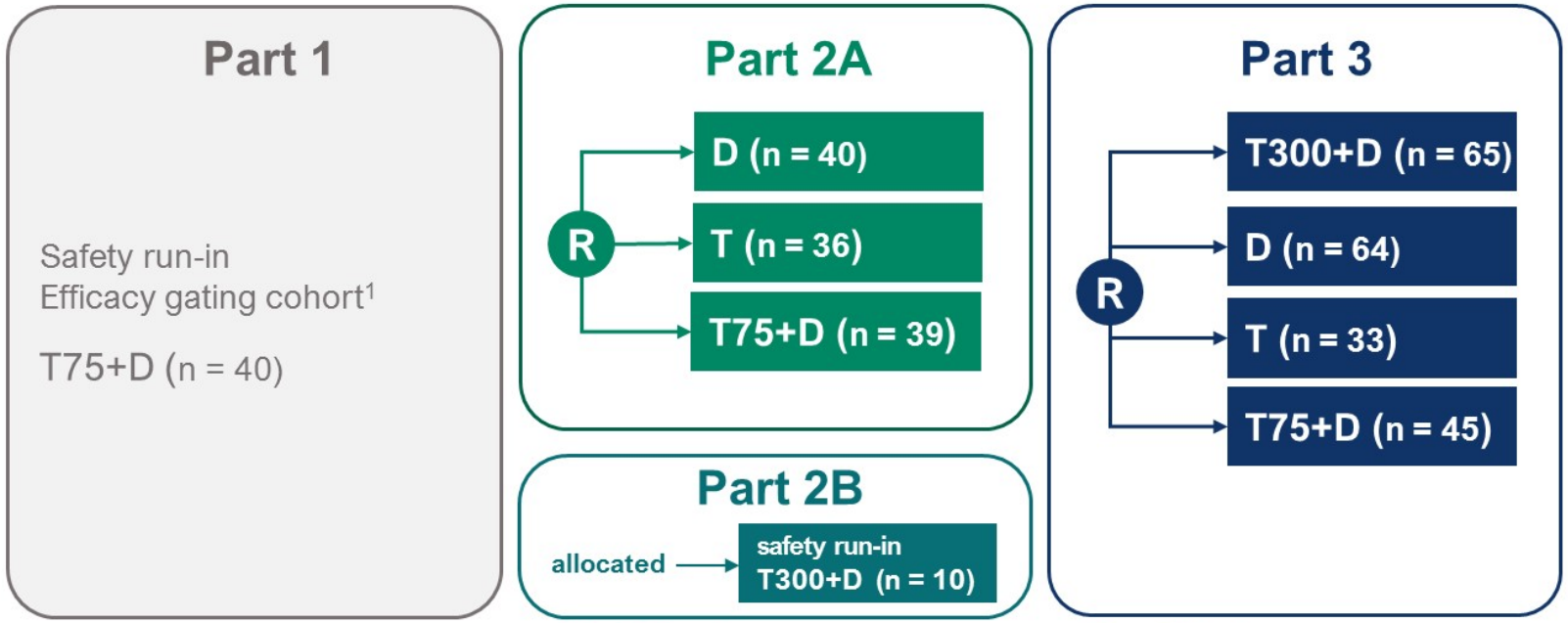
Yau, et al, GI ASCO 2020

COSMIC-312: Cabozantinib/Atezolizumab vs sorafenib in treatment-naive advanced HCC



Kelley, et al, *Future Oncology,* 2020

Study 22: Tremelimumab (T) in Combination with Durvalumab (D) for Advanced HCC



Key Milestones

FSI Part 2A	February 2017
FSI Part 2B	October 2017

Key Milestones

FSI Part 3	February 2018
LSI Part 3	April 2019

Treatments and Regimens

T300+D	tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W
D	durvalumab 1500 mg Q4W
T	tremelimumab monotherapy 750 mg Q4W × 7 doses, Q12W thereafter
T75+D	tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W

Key Eligibility

- Unresectable HCC with fresh or archival tumor biopsy sample available
- Progressed on, intolerant to, or refused prior sorafenib
- Child Pugh A liver function

Objectives and Assessments

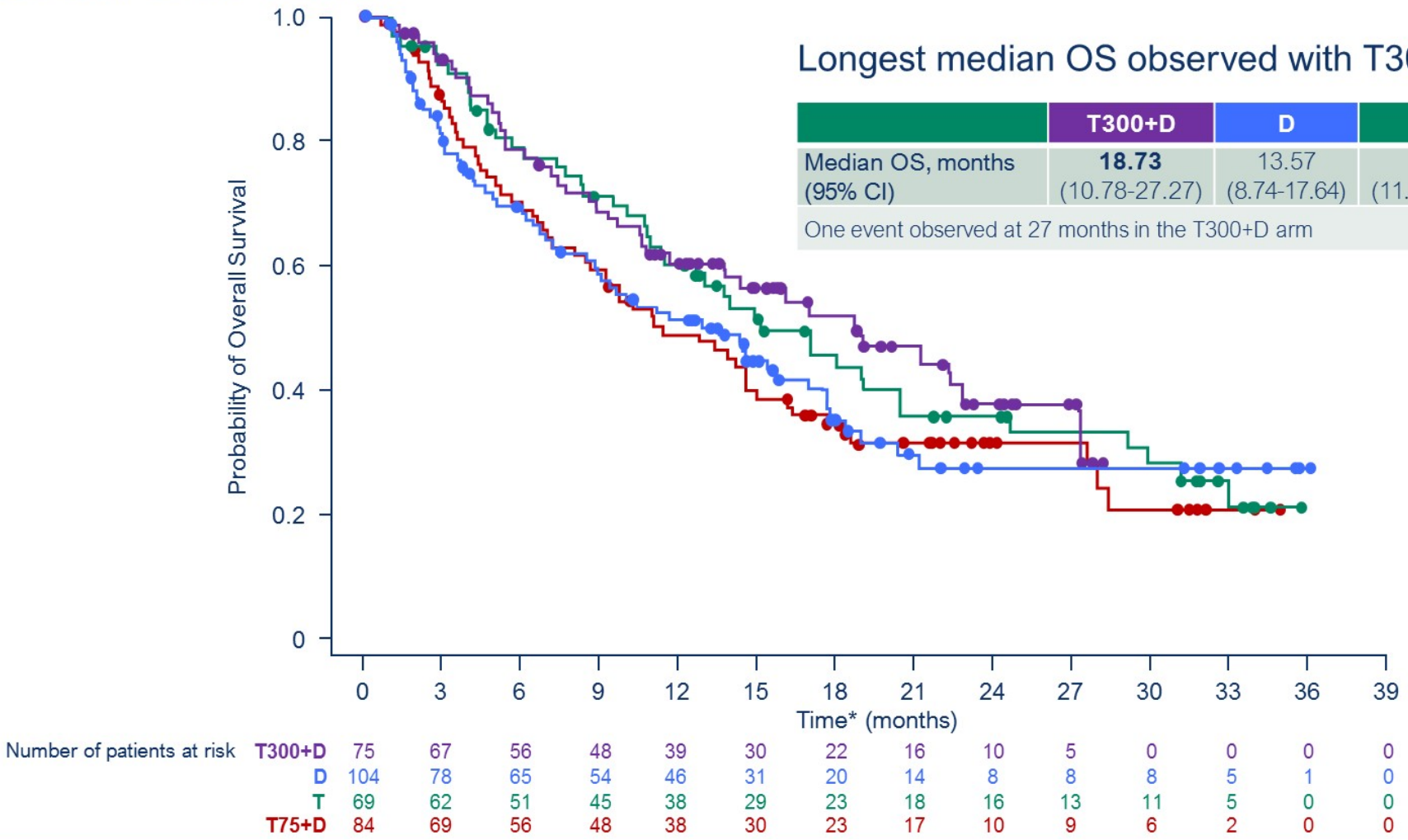
Primary Endpoint: Safety

Key Secondary Endpoints
- Overall survival
- Objective response rate
- Duration of response

Key Assessments
- Multiphase imaging Q8 weeks
- Circulating immune cells
- PD-L1 status (Ventana SP263)

Sangro, et al, GI ESMO 2020; Kelley, et al, ASCO 2020

Study 22: Overall Survival



Longest median OS observed with T300+D

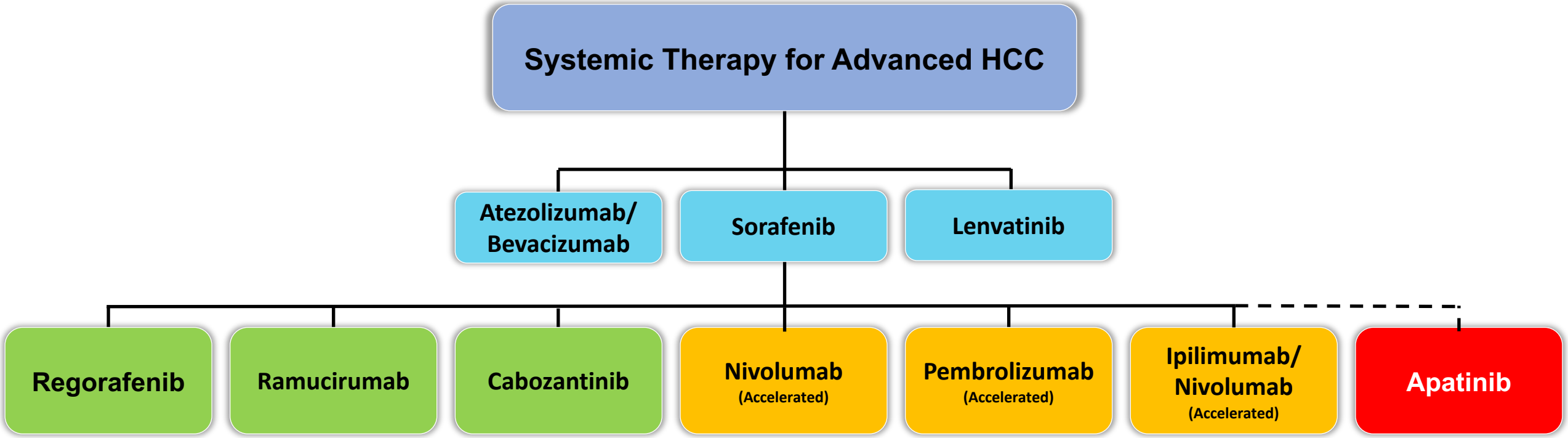
	T300+D	D	T	T75+D
Median OS, months (95% CI)	**18.73** (10.78-27.27)	13.57 (8.74-17.64)	15.11 (11.33-20.50)	11.30 (8.38-14.95)

One event observed at 27 months in the T300+D arm

Sangro, et al, GI ESMO 2020; Kelley, et al, ASCO 2020

Conclusions: Combination Systemic Therapy for HCC

- Clinical Implications:
  - Multiple combination regimens are showing promise in patients with advanced HCC
  - Responses observed regardless of PD-L1 or viral status
  - Rates of hepatotoxicity do not appear to be significantly higher than in other cancers
- Future Directions:
  - Results of these trials have led to multiple ongoing Phase III trials, and results are awaited
  - Better predictive biomarkers are needed
  - Better understanding priming of the immune system may impact clinical trial design and improve outcomes
  - Moving these strategies to the neoadjuvant setting and in combination with local therapies may provide benefit to patients with earlier stage disease



- Multiple new treatments on the horizon which are likely to expand options and raise questions about which to choose and how to sequence
- Predictive biomarkers are urgently needed to better match patients to drugs that will benefit them
- Multiple new trials combining liver directed therapy with systemic therapy could change the treatment paradigm for BCLC stage B and C HCC